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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/203,500	12/01/98	HONOLD K	P564-8025

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NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
655 FIFTEENTH STREET NW
SUITE 330-G STREET LOBBY
WASHINGTON DC 20005-5701

EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	5

DATE MAILED: 06/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/203,500	Applicant(s) Honold et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Dec 1, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-19* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

3. A sequence appears at page 36 of the Specification which lacks a sequence identifier. Correction is required.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 7, 8, 11, 13-16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1, 8, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The final correlation or recapitulation step is missing which restates the preamble.

7. Claim 7 appears to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

8. The phrase in claim 11, line 2, "a process" is indefinite because the use of "a" to refer to the process implies that one process among many others is being chosen. It is unclear how these processes may differ one from the other. Deleting "a" and inserting --the-- would cure this defect.

9. Claims 13 and 19 recite the limitation "characterized". This term is indefinite since it does not provide the skilled practitioner with a clear definition of the metes and bounds of the claimed subject matter. A characterization may not be complete and thorough in its description of a subject, but a mere recitation of an observation or property pertaining to the subject.

10. Claim 15, line 5, recites "a third vector". There is no claimed ***second*** vector, making the claimed "third vector" unclear as to how it fits into the scheme of the claim.

11. Claim 16 recites the limitation "partial sequences" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO94/17176 in view of WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al.

The claims are drawn to a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell (which cell may be a human cell) by transfecting the cell with a vector which comprises an expression control sequence and a first

amplification gene and a positive selective marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination. The cell may be DHFR-negative and the homologous flanking sequences may be DHFR sequences. The recombinase site-specific sequences may be LoxP sequences. A negative selection marker may be located outside the homologous recombination sequences. The nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase. The expression control sequence may be a HIF-binding nucleic acid sequence. A second vector which has a construct as described above which contains a gene encoding DHFR may be transfected into the cell.

WO97/37012 taught (see especially the abstract, the summary, the claims, the Figures and pages 12-22) a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell by transfecting the cell with a vector which comprises an expression control sequence and a first amplification gene and a positive selective marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination. The recombinase site-specific sequences may be LoxP sequences. A negative selection marker may be located outside the homologous recombination sequences. The nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase. The expression control sequence may be a hypoxia-induced nucleic acid sequence.

WO94/17176 did not teach that the cell may be DHFR-negative and the homologous flanking sequences may be DHFR sequences, nor that the expression control sequence may be a HIF-binding nucleic acid sequence, nor that a second vector which has a construct as described above which contains a gene encoding DHFR may be transfected into the cell.

WO94/37012 (see especially the abstract, the summary, the Figures the claims and pages 12-15 and 22) and WO96/29411 (see especially the abstract, the summary , the Figures, the claims and pages 19-23) taught the insertion by homologous recombination of an expression controlling nucleic acid element into the genome of a cell adjacent to a gene of interest, where the construct encoded a gene for DHFR.

Cruz et al. taught (see the entire article) the insertion of a construct into a host genome where the homologous flanking sequences were DHFR sequences, the host cell was DHFR-negative.

US Pat. No. 5,695,977 taught (see especially the abstract, the claims, the Figures and columns 2-8) the insertion of an enhancer construct into a host genome by homologous recombination where the encoded marker sequence was flanked by recombinase sites, and where positive and negative markers facilitated the insertion, selection and marker removal process.

Mazure et al. taught (see especially the abstract, the introduction, the Figures, and materials and methods) the use of a construct which encoded an HIF-binding nucleic acid to control genes associated with cellular responses to hypoxia.

It would have been obvious to one of skill in the art at the time of the instant invention to combine the teachings of WO94/17176 with WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al. to produce the instant invention because WO94/12650 taught a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell (which cell may be a human cell) by transfecting the cell with a vector which comprises an expression control sequence and a first amplification gene and a positive selective marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination. The recombinase site-specific sequences may be LoxP sequences. A negative selection marker may be located outside the homologous recombination sequences. The nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase. The entire concept of the instant claimed invention is embraced by the teachings of WO94/12650. Limitations such as using DHFR negative cells with a DHFR encoding vector, and DHFR flanking homologous sequences to target the insertion of the construct/vector into the genome of a host cell, and the introduction of an expression control sequence such as HIF-binding nucleic acid sequences adjacent to an endogenous gene in the host genome were all well known techniques for gene manipulation in a host cell, as taught by WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al. above. WO97/37012 taught the introduction of a hypoxia induced expression control sequence into a region of a desired gene in a host genome.

Cruz et al. and WO94/37012 taught the application of DHFR to the introduction of a construct for controlling expression into a host cell and a host cell genome.

One of skill in the art would have been motivated at the time of the instant invention to combine the teachings of WO94/17176 with WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al. to produce the instant invention because WO94/12650 taught a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell (which cell may be a human cell) by transfecting the cell with a vector which comprises an expression control sequence and a first amplification gene and a positive selective marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination. The recombinase site-specific sequences may be LoxP sequences. A negative selection marker may be located outside the homologous recombination sequences. The nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase. The entire concept of the instant claimed invention is embraced by the teachings of WO94/12650. Limitations such as using DHFR negative cells with a DHFR encoding vector, and DHFR flanking homologous sequences to target the insertion of the construct/vector into the genome of a host cell, and the introduction of an expression control sequence such as HIF-binding nucleic acid sequences adjacent to an endogenous gene in the host genome were all well known techniques for gene manipulation in a host cell, as taught by WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al. above. WO97/37012 taught the introduction of a

hypoxia induced expression control sequence into a region of a desired gene in a host genome. Cruz et al. and WO94/37012 taught the application of DHFR to the introduction of a construct for controlling expression into a host cell and a host cell genome. Studies of host genomes by manipulation of DHFR genes such as employed in the instant claimed invention are taught in Cruz et al. at page 173, columns 1 and 2 which show the advantages of integrating vector DNA into the host genome at DHFR loci, and also where the host cells are DHFR defective. At page 11, lines 19 bridging to page 12, line 2 WO94/37012 states "[t]he promoter may regulate the expression of a gene constitutively, or differentially with respect to the tissue in which expression occurs or , with respect to the developmental stage at which expression occurs, or in response to external stimuli such as physiological stresses...such as those induced by anaerobiosis or hypoxia". One of skill in the art would therefore be motivated to combine the teachings of WO94/17176 with WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of WO94/17176 with WO96/29411, WO94/12650, WO97/37012, US Pat. No. 5,695,977, Cruz et al. and Mazure et al.

Conclusion

14. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or

applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
May 24, 1999

NANCY DEGEN
PRIMARY EXAMINER